

CLAIMS

1. A method of detecting an agent that modulates the activity of CCRL2, the method comprising:

(a) contacting a CCRL2 polypeptide with a macrophage inflammatory protein-4 (MIP-4) polypeptide in the presence of a candidate agent under conditions, which in the absence of the test agent, permit the binding of the MIP-4 polypeptide to the CCRL2 polypeptide; and

(b) determining whether the candidate agent is capable of modulating the interaction between said CCRL2 polypeptide and said MIP-4 polypeptide.

2. A method according to claim 1, wherein the MIP-4 polypeptide is a polypeptide comprising:

(a) the sequence shown in SEQ ID NO: 6; or

(b) a sequence which is at least 50% identical to SEQ ID NO: 6 and which binds to and activates a signalling activity of CCRL2; or is a fragment of SEQ ID NO: 6 which binds to and activates a signalling activity of CCRL2.

3. A method according to claim 1 or 2, wherein the CCRL2 polypeptide is a polypeptide comprising:

(a) the sequence shown in SEQ ID NO: 2 or 4;

(b) a sequence which is at least 80% identical to SEQ ID NO: 2 or 4 over its entire length and functionally equivalent to CCRL2.

(c) a fragment of SEQ ID NO: 2 or 4 which is functionally equivalent to CCRL2.

4. A method according to any one of the preceding claims, wherein the candidate agent is a polypeptide, an antibody or antigen-binding fragment thereof, a lipid, a carbohydrate, a nucleic acid or a chemical compound.

5. A method according to any one of the preceding claims, wherein step (b) comprises monitoring binding of the CCRL2 polypeptide to the MIP-4 polypeptide.

6. A method according to claim 5, wherein the binding of the CCRL2 polypeptide to the MIP-4 polypeptide is monitored using label displacement, surface plasmon resonance, fluorescence resonance energy transfer, fluorescence quenching

or fluorescence polarization.

7. A method according to any one of the preceding claims, wherein the MIP-4 polypeptide is detectably labelled.

8. A method according to claim 7, wherein the MIP-4 polypeptide is detectably labelled with a moiety is a radioisotope, a fluorophore, a quencher of fluorescence, an enzyme, an affinity tag or an epitope tag.

9. A method according to any one of claims 1 to 4, wherein step (b) comprises monitoring the signalling activity of the CCRL2 polypeptide.

10. A method according to claim 9, wherein the signalling activity is monitored by measurement of guanosine nucleotide binding, GTPase activity, adenylate cyclase activity, cyclic adenosine monophosphate (cAMP), Protein Kinase C activity, phosphatidylinositol breakdown, diacylglycerol, inositol triphosphate, intracellular calcium, MAP kinase activity or reporter gene expression.

11. A method according to claim 10, wherein the signalling activity is monitored by measuring the activity of Gi3.

12. A method according to any one of claims 1 to 4, wherein step (b) comprises monitoring the chemotactic activity of the CCRL2 polypeptide.

13. A method according to any one of the preceding claims, wherein the CCRL2 polypeptide is expressed on a cell.

14. A method according to claim 13, wherein the cell is a yeast cell.

15. A method according to claim 14, wherein the yeast cell comprises a G protein in which at least 5 amino acids at the carboxy terminal of a yeast G subunit have been replaced with the corresponding residues from a non-yeast G protein.

16. A method according to claim 15, wherein the non-yeast G-protein is Gi3.

17. A method according to any one of claims 1 to 11, wherein the CCRL2 polypeptide is present:

- (a) in or on synthetic liposomes;
- (b) in or on virus-induced budding membranes;
- (c) in or on an artificial lipid bilayer; or
- (c) in a membrane fraction from cells expressing the CCRL2 polypeptide.

18. An agent detected by a method according to any one of the preceding claims.
19. An antibody specific for MIP-4, which antibody is capable of inhibiting binding of MIP-4 to CCRL2.
- 5 20. An antibody specific for CCRL2, which antibody is capable of inhibiting binding of CCRL2 to MIP-4.
21. A method of modulating the activity of a CCRL2 polypeptide in a cell, the method comprising delivering an agent according to claim 18 or an antibody according to claim 19 or 20 to the cell, such that the activity of CCRL2 is modulated.
- 10 22. A method according to claim 21, wherein the cell is *in vitro*.
23. A pharmaceutical composition comprising an agent according to claim 18 or an antibody according to claim 19 or 20 and a pharmaceutically acceptable carrier or diluent.
- 15 24. A method for treating an inflammatory disease or disorder, a disease or disorder associated with enhanced macrophage activity or an infection, the method comprising administering a therapeutically effective amount of an agent according to claim 18, an antibody according to claim 19 or 20 or a pharmaceutical composition according to claim 23 to an individual in need thereof.
- 20 25. A method according to claim 24, wherein the inflammatory disease or disorder is chronic obstructive pulmonary disease (COPD), bronchitis, emphysema, an inflammatory bone disorder, psoriasis, inflammatory bowel disease, an inflammatory brain disorder, atherosclerosis, endometriosis, autoimmune deficiency syndrome (AIDS), lupus erythematosus, allograft rejection, rheumatoid arthritis or allergic inflammation, or wherein the disease or disorder associated with enhanced
- 25 macrophage activity is obesity, obesity-related insulin resistance, autoimmune disease, contact hypersensitivity or cancer.
26. An agent according to claim 18, an antibody according to claim 19 or 20 or a pharmaceutical composition according to claim 21 for use in a method of treatment of a human or animal body by therapy.
- 30 27. Use of an agent according to claim 18 or an antibody according to claim 19 or 20 in the manufacture of a medicament for the treatment of an inflammatory disease or disorder, a disease or disorder associated with enhanced

macrophage activity or an infection.

28. A use according to claim 27, wherein the inflammatory disease or disorder is chronic obstructive pulmonary disease (COPD), bronchitis, emphysema, an inflammatory bone disorder, psoriasis, inflammatory bowel disease, an inflammatory brain disorder, atherosclerosis, endometriosis, autoimmune deficiency syndrome (AIDS), lupus erythematosus, allograft rejection, rheumatoid arthritis or allergic inflammation, or wherein the disease or disorder associated with enhanced macrophage activity is obesity, obesity-related insulin resistance, autoimmune disease, contact hypersensitivity or cancer.

29. A method of activating a CCRL2 signalling pathway in a cell, the method comprising delivering, to the cell, a polypeptide comprising:

- (a) the MIP-4 sequence shown in SEQ ID NO: 6; or
- (b) a sequence at least 50% identical to SEQ ID NO: 6 and which binds to and activates a signalling activity of CCRL2; or
- (c) a fragment of SEQ ID NO: 6 which binds to and activates a signalling activity of CCRL2.

30. A method according to claim 29, wherein the cell is *in vitro*.

31. Use of a polypeptide comprising:

- (a) the MIP-4 sequence shown in SEQ ID NO: 6; or
- (b) a sequence at least 50% identical to SEQ ID NO: 6 and which binds to and activates a signalling activity of CCRL2; or
- (c) a fragment of SEQ ID NO: 6 which binds to and activates a signalling activity of CCRL2, a polynucleotide encoding said polypeptide, or an antibody which binds to said polypeptide for the manufacture of a medicament for treating a CCRL2-related disease or disorder.

32. A use according to claim 31, wherein the CCRL2-related disease or disorder is inflammatory bowel disease, endometriosis, atherosclerosis or an inflammatory brain disorder.

33. Use of a polypeptide comprising:

- (a) the CCRL2 sequence shown in SEQ ID NO: 2 or 4;
- (b) a sequence which is at least 80% identical to SEQ ID NO: 2 or 4 over its entire length and is functionally equivalent to CCRL2; or

(c) a fragment of SEQ ID NO: 2 or 4 which is functionally equivalent to CCRL2, a polynucleotide encoding said polypeptide, or an antibody which binds to said polypeptide for the manufacture of a medicament for treating a MIP-4-related disease or disorder.

5 34. A use according to claim 33, wherein the MIP-4-related disease or disorder is allergic inflammation or cancer.

 35. A method of diagnosing a CCRL2-related disease or disorder in an individual, the method comprising:

 (a) carrying out an amplification reaction on a sample isolated from the
10 individual using primers specific for a polynucleotide encoding a MIP-4 polypeptide; and

 (b) determining the presence or absence of a polynucleotide encoding a MIP-4 polypeptide in the sample and thereby determining the presence of a CCRL2-related disease or disorder in the individual.

15 36. A method according to claim 35, further comprising comparing the amount of the amplified polynucleotide encoding a MIP-4 polypeptide produced in step (a) with a standard, wherein a difference in the amount relative to the standard is indicative of the presence of a CCRL2-related disease or disorder in the individual.

 37. A method of diagnosing a CCRL2-related disease or disorder in an
20 individual, the method comprising:

 (a) amplifying a polynucleotide encoding a MIP-4 polypeptide, using a nucleic acid isolated from the individual as a template; and

 (b) determining whether the polynucleotide comprises a polymorphism associated with a CCRL2-related disease or disorder.

25 38. A method according to claim 33, wherein step (b) comprises:

 (a) inputting MIP-4 sequence data from the individual to a computer system;

 (b) comparing said sequence data to a computer database, which database comprises information relating MIP-4 sequence data to a CCRL2-related disease or
30 disorder; and

 (c) determining on the basis of said comparison whether the MIP-4 polynucleotide comprises a polymorphism associated with a CCRL2-related disease

or disorder.

39. A method of diagnosing a CCRL2-related disease or disorder in an individual, the method comprising:

(a) contacting a sample isolated from the individual comprising a CCRL2 polypeptide with a MIP-4 polypeptide under conditions which permit the binding of the MIP-4 polypeptide to the CCRL2 polypeptide;

(b) measuring the activity of the CCRL2 polypeptide; and

(c) comparing the activity of the CCRL2 polypeptide with a standard, wherein a difference in the activity relative to the standard is indicative of the presence of a CCRL2-related disease or disorder in the individual.

40. A method according to claim 39, wherein step (b) comprises monitoring:

(i) the signalling activity of the CCRL2 polypeptide; or

(ii) the chemotactic activity of the CCRL2 polypeptide.

41. A method according to any one of claims 35 to 40, wherein the MIP-4 polypeptide is a polypeptide comprising:

(a) the sequence shown in SEQ ID NO: 6; or

(b) a sequence at least 50% identical to SEQ ID NO: 6 and which binds to and activates a signalling activity of CCRL2; or

(c) a fragment of SEQ ID NO: 6 which binds to and activates a signalling activity of CCRL2.

42. A method according to any one of claims 35 to 40 wherein the CCRL2-related disease or disorder is inflammatory bowel disease, endometriosis, atherosclerosis or an inflammatory brain disorder.

43. A kit for detecting an agent that modulates the activity of CCRL2, the kit comprising: (i) a MIP-4 polypeptide; and (ii) a CCRL2 polypeptide or a polynucleotide encoding a CCRL2 polypeptide.

44. A kit according to claim 43, which comprises a cell transformed with a polynucleotide encoding a CCRL2 polypeptide.

45. A kit according to claim 43, wherein the CCRL2 polypeptide is present in a cell membrane fraction, a synthetic liposome or a virus-induced budding membrane.

46. A kit according to any one of claims 43 to 45, wherein the MIP-4 polypeptide is a polypeptide comprising:

- (a) the sequence shown in SEQ ID NO: 6; or
- (b) a sequence at least 50% identical to SEQ ID NO: 6 and which binds to
5 and activates a signalling activity of CCRL2; or
- (c) a fragment of SEQ ID NO: 6 which binds to and activates a signalling activity of CCRL2.